REMARKS

Claims 1, 3-10, and 16-23 are pending in the application after entrance of the Preliminary Amendment, filed January 9, 2009. Claims 1, 3-10 and 16-23 stand rejected by the Examiner. Applicant respectfully requests reconsideration of this case. The remaining rejection in this case is addressed below.

Rejections under 35 USC § 103

Claims 1, 3-10, and 16-23 remain rejected under 35 USC § 103(a) as being obvious over *Oeltgen et al.* (US 6,645,938) in view of *Motterlini et al.* (Circulation Research, 2002). The Examiner asserts that *Oeltgen et al.* teaches methods and compounds for protecting organs against ischemia and reperfusion injury. The Examiner admits that *Oeltgen et al.* does not teach the use of a metal carbonyl compound which makes available carbon monoxide, for organ protection. The Examiner alleges that "this deficiency is cured by the teachings of *Motterlini et al.*" According to the Examiner, *Motterlini et al.* teaches that "$[Ru(CO)_3Cl_2]_2$ freshly dissolved in DMSO releases CO into the solution" and "CO releasing compounds have been found to be pivotal in the defensive system against ischemia-reperfusion damage. (see page 17, column 1, paragraph 1)." Applicant respectfully submits that there is no motivation, suggestion , or teaching to combine these two references to render the claimed invention obvious.

Oeltgen et al. teaches that a peptide (compound-D) may be used in a preservative solution for protecting organs against ischemia and reperfusion injury. According to *Oeltgen et al.*, compound-D may work by opening or activation of K_{ATP} channels (column 6, lines 20-21). In no way, does *Oeltgen et al.* teach a compound that releases CO. *Oeltgen et al.* does not teach or suggest any compound other than compound-D, a peptide. *Oeltgen et al.* does not provide one of ordinary skill in the art with a reason or motivation to use a compound other than compound-D in organ protection. *Oeltgen et al.* does not even remotely suggest that CO releasing compounds would have a similar effect as compound-D. *Oeltgen et al.* does not provide one of ordinary skill in the art with any reason or motivation to use a transition metal carbonyl compound that releases CO, instead of compound-D. Applicant is at a loss as to why the Examiner thinks that one of ordinary skill in the art would ever combine *Oeltgen et al.* with *Motterlini et al.* to come up with claimed invention. The

agents used in these references are chemically different (one is a peptide, the other is an organometallic complex), and they are thought to act differently (one by activation of K_{ATP}, the other by the release of CO). Applicant believes the Examiner has impermissibly used the specification of the instant application to combine prior art references and construct the claimed invention.

The Examiner states that *Motterlini et al.* teaches that "the transition metal carbonyls taught are useful for defense against ischemia-reperfusion damage". Applicant respectfully disagrees. *Motterlini et al.* teaches transition metal carbonyl complexes as CO-releasing molecules that could mimic the pharmacological action of heme oxygenase-derived CO. *Motterlini et al.* "identifies a novel group of substances [three transition metal carbonyl complexes] that are capable of carrying and delivering CO, In a similar fashion to endogenous HO-1-derived CO, CO-RMS also exert biological activities by eliciting vascular relaxation and mitigating both coronary vasoconstriction and acute hypertension." *Motterlini et al.* does not teach or suggest that the metal carbonyl complexes under investigation could be used in a composition for protecting an isolated organ from damage as claimed.

Based on the teachings of *Motterlini et al.* and *Oeltgen et al.*, one of ordinary skill in the art would have no reason or motivation to try or investigate the effects of carbon monoxide (CO) from metal carbonyl complexes on ischemia and reperfusion injury. As it was not known, and *Oeltgen et al.* does not teach or suggest, that CO has any effect on the opening of K_{ATP} channels, there would have been no reasonable expectation of success in replacing compound-D with a transition metal complex capable of releasing CO.

The passage of *Motterlini et al.* cited by the Examiner (page 17, column 1, paragraph 1), refers to the role of heme oxygenase (HO-1), an endogenous biological molecule, as a defensive system against stressful stimuli such as ischemia-reperfusion damage:

> "The main endogenous source of CO is heme oxygenase, which exists in constitutive (HO-2 and HO-3) and inducible (HO-1) isoforms; heme serves as substrate for HO-1 and HO-2 in the formation of CO, free ferrous iron, and biliverdin, the latter being rapidly converted to bilirubin by biliverdin reductase. There is general consensus, supported by extensive published reports, that HO-1 represents a pivotal inducible defensive system against

> stressful stimuli, including UVA radiation, carcinogens, ischemia-reperfusion damage, endotoxic shock, and several other conditions characterized by production of oxygen-derived free radicals."

The Examiner has generalized this statement: "*Motterlini et al.* teach that CO releasing compounds have been found to be pivotal in the defensive system against ischemia-reperfusion damage." This is not taught or suggested by *Motterlini et al.,* and the Examiner's generalization regarding the use of all CO releasing compounds is not justified.

The Examiner also asserts that *Motterlini et al.* teaches that "the transition metal carbonyls taught are useful for defense against ischemia-reperfusion damage." There is no basis in *Motterlini et al.* to support the Examiner's assertion. *Motterlini et al.* does not teach or suggest that the metal carbonyl compounds could be used in a composition for protecting an isolated organ from damage. *Motterlini et al.* focuses on the vasodilatory effects of metal carbonyl compounds and suggests their use to alleviate vascular and immuno-related dysfunctions (see abstract).

The instant application is the first demonstration that carbon monoxide released *in vivo* by metal carbonyl compound can effectively prevent ischemic injury. Without the information provided in the present application, one of ordinary skill in the art would not consider using metal carbonyl compounds in a composition for protection of an extracorporeal organ or an isolated organ that is inside or attached to the body.

The Examiner has not provided a clear and reasonable argument why one of ordinary skill in the art would use the metal carbonyl compounds of *Motterlini et al.* in a solution such as that taught by *Oeltgen et al.* to protect an extracorporeal organ or an isolated organ from ischemic injury let alone have a reasonable expectation of success in doing so. The only way to arrive at the Examiner's combination of these references is through the application of hindsight reconstruction of Applicant's invention based on the teachings in Applicant's specification. This is improper.

The Examiner asserts that it is his "position that one of ordinary skill in the art would be motivated to combine the carbon monoxide-releasing molecules of *Motterlini et al.* with the composition taught by *Oeltgen et al.* in order to give an additive effect of both the peptide molecule and the carbon monoxide-releasing molecule in protecting against ischemia-reperfusion damage." Applicant's invention does not relate to the combination of a carbon monoxide-releasing molecule

with compound-D or any other peptide molecule. The claimed invention does not relate to a combination at all. The instant invention relates to a "composition including a metal carbonyl compound [...] wherein the metal carbonyl [...] makes available carbon monoxide to limit post-ischaemic damage[...]." The Examiner's point regarding a combination with compound-D is confusing and irrelevant to the instant invention.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under § 103.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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